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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,543	09/20/2006	Anders Eriksson	06275-522US1 101414-1P US	4480

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
02/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/593,543	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

Applicant's election without traverse of the invention of Group II, Claims 1-12, 15 and 18-28, drawn to compounds of Formula (I) in which G1 is phenyl, process for preparation thereof, pharmaceutical compositions thereof, and methods of treating disease therewith, in the Response filed on March 11, 2008 is acknowledged.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10, 15, 18, 19-24, 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that the specification did not describe in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The originally recited "thiol" identifies a compound not a substituent. The application as filed offers no definition or exemplification of the group "mercapto."

Claims 15 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating asthma or chronic

obstructive pulmonary disease (COPD) (claims 15 and 28). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following reasons apply to this enablement rejection.

The instant claims cover asthma and COPD mediated by compounds of claim 1 or claim 18, for which insufficient enablement is provided.

At present no known drug can successfully prevent or reverse the course of COPD. See European Respiratory Society, http://www.newtocopd.com/currentaffairsnews/list751_item17680.aspx, downloaded 1/15/2008, stating, "… there are currently no effective treatments for COPD …"

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). See *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding testing types needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. This disclosure is not sufficient to enable the claimed methods based solely on the disclosed activity.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue

experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration to determine whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) claim breadth; (2) nature of the invention; (3) state of the prior art; (4) level of predictability in the art; (5) amount of direction provided by the inventor; (6) presence of working examples; and (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (CAFC 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement.

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover pharmaceutical methods using thousands of substituted 1,2,4-triazol-3-one compounds of Formula (I).

(b) Scope of the diseases covered. The diseases construed by the claims have been described above. The specification fails to identify results of treatment with the methods of this invention or provided prior art teachings which support a direct, correlative connection between MMP inhibition and the treatment of asthma and COPD and how one would recognize such results.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** The art indicates the need for undue experimentation.

The discussion above of Europ. Resp. Soc. is repeated here as equally pertinent.

Molet, et al., Inflamm. Res. 54 (2005) 31-36, merely suggests MMP-12 inhibition as an area of possible study in COPD and emphysema, "… this study demonstrated patients with COPD produce greater quantities of MMP-12 than controls, which may be a critical step in the pathogenesis of emphysema."

Tjwa, et al., Circulation 113 (16):1929 (2006) disappointingly report:

> Because of their key roles in tissue remodeling and cell infiltration, MMP inhibitors have been considered attractive drug targets. However, most preclinical and clinical studies did not yield the expected result, in part because nonselective inhibitors were used, and several of these MMPs have pleiotropic, sometimes even opposite activities. These failures should not necessarily remove all hope that more selective MMP inhibitors (as have been developed recently for MMP-12) might ever become clinically useful.

This specification (p. 40, *inter alia*) reports that these MMP inhibitors are nonselective inhibitors of MMP2, MMP8, MMP9, MMP12, MMP14 and MMP19. The ability of an agent that exhibits activities shown in the specification to treat all diseases-conditions construed by the claims remains open to further study and proof.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests to show a correlation between MMP inhibition and treatment of conditions recited for the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.

6. **Skill of those in the art:** Europ. Respir. Soc., Molet and Tjwa call into question the ability of a single class of compounds to effectively treat asthma and COPD; they confirm the need for additional research.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed herein, indicates the requirement for undue experimentation.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

Response to Remarks of 11-21-2008

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. The more familiar terms 'chronic bronchitis' and 'emphysema' are no longer used, but are now included within the COPD diagnosis. COPD is not simply a "smoker's cough" but an under-diagnosed, life-threatening lung disease.

Asthma is a lung disease affecting bronchial tubes or airways; reversible obstructive airway disease. Unlike other airway obstructing conditions, e.g., cystic fibrosis, chronic bronchitis, emphysema, asthma does not affect sufferers all the time. During an asthma attack, membranes inside bronchial tubes release mucus and become inflamed, causing muscles to contract and create wheezing spasms. Attacks can be severe or relatively mild, but the condition is dangerous and can easily spiral out of control. Specific causes of asthma are not straightforward. Asthma divides into many different types:

- **Allergic Asthma:** Triggered by allergens, e.g., pet dander, pollen, dust mites, pollutants, wood dust, smoke, irritants, chemicals, viral infections, bacteria, stress, emotion, exercise.
- **Childhood Allergic Asthma:** Maternal smoking can contribute to asthma or other infant lung function impairment, even before a child is born. Continued exposure to

cigarette smoking can irritate the respiratory tract, making infants and children particularly vulnerable to allergic asthma.

- **Intrinsic Asthma:** Allergies are not involved; typical onset occurs after 40. Possible causes include respiratory irritants, e.g., perfumes, cleaning agents, fumes, smoke, cold air, upper respiratory infections, gastroesophageal reflux. Intrinsic asthma is less responsive to treatment than allergic asthma.
- **Exercise-Induced Asthma:** Can affect anyone at any age; may be attributed to loss of heat and moisture in the lungs with strenuous exercise. Frequent coughing during exercise may be the only symptom, but exercise-induced asthma symptoms can be more severe in cold, dry conditions. Prophylactic medications can prevent asthmatic symptom onset for sensitive individuals.
- **Nocturnal Asthma:** Affects people during sleep, regardless of time of sleep. Symptoms can be triggered by allergens in bedding or the bedroom, decrease in room temperature and gastroesophageal reflux.
- **Occupational Asthma:** Occurs as a result of breathing chemical fumes, wood dust or other irritants over long periods of time.
- **Steroid-Resistant Asthma:** Overuse of asthma medications can lead to status asthmaticus, a severe asthma attack that fails to respond to medication and may require mechanical ventilation.

Applicants cite *Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.*, 75 USPQ2d 1865 (Fed. Cir. 2005), on the issue of the sufficiency of enablement. Although the *Warner-Lambert* language offers legal guidance, the Federal Circuit found it

necessary to remand, so this case offers no factual guidance on the issue of sufficiency of enablement.

Lowrey, et al., Respiratory Med. (2008) 102, 845-851, noting that MMP-9 protein level does not reflect overall MMP activity in airways of COPD patients, summarizes:

> … we have examined MMP activity by a variety of methods in induced sputum in patients with stable COPD and smokers without COPD. Despite increased MMP-9 protein, total MMP activity was not higher in sputum from COPD subjects. These findings may reflect raised levels of MMP inhibitors or a reduction in the activation of MMPs during stable disease, however, we have not been able to demonstrate this in the current study. Our findings suggest that the activity of MMPs in COPD may be more complex than previously thought and that the balance between MMPs and TIMPs [tissue inhibitors of matrix metalloproteinases], the course of disease including exacerbations, site of MMP activity and the overall effect on proteolytic activity needs to be considered when investigating airway inflammation.

This specification (p. 40, *inter alia*) reports that these MMP inhibitors are nonselective inhibitors of MMP2, MMP8, MMP9, MMP12, MMP14 and MMP19.

Turino, Chest, 2007: 132; 1724-1725, in studying proteases in COPD, emphasizes the need for further research:

> Additional insights into the immunogenicity of elastin peptides that result from protease degradation in the lung parenchyma indicate their possible role in creating autoimmune mechanisms that can perpetuate the inflammatory state of the lung in COPD. Such mechanisms may explain the persistence and progression of COPD after smoking cessation or other initiating factors. Proteases therefore may be responsible for additional pathogenic mechanisms in COPD other than tissue degradation. Overall, the further investigation of metalloproteases deserves intense investigation *in vivo* in COPD patients going forward and is essential to develop significant therapies for this disease.

Applicants cite *In re Wright*, 27 USPQ2d 1510, 1512 (Fed. Cir. 1993) regarding the requirements to reject a claim for lack of enablement under 35 USC 112, par. 1. The Federal Circuit affirmed the BPAI in *Wright*, because, as in the present case, the

PTO set forth a reasonable basis for finding that the scope of the rejected claims is not enabled by the specification.

In this case, the article cited by Europ. Resp. Soc., http://www.newtocopd.com/currentaffairsnews/list751_item17680.aspx, downloaded 1/15/2008, supports that, "… there are currently no effective treatments for COPD …"

Molet, et al., Inflamm. Res. 54 (2005) 31-36, merely suggests MMP-12 inhibition as an area of possible study in therapy for COPD and emphysema, "… this study demonstrated patients with COPD produce greater quantities of MMP-12 than controls, which may be a critical step in the pathogenesis of emphysema."

Tjwa, et al., Circulation 113 (16):1929 (2006) disappointingly report:

> Because of their key roles in tissue remodeling and cell infiltration, MMP inhibitors have been considered attractive drug targets. However, most preclinical and clinical studies did not yield the expected result, in part because nonselective inhibitors were used, and several of these MMPs have pleiotropic, sometimes even opposite activities. These failures should not necessarily remove all hope that more selective MMP inhibitors (as have been developed recently for MMP-12) might ever become clinically useful.

This specification (p. 40, *inter alia*) reports that these MMP inhibitors are nonselective inhibitors of MMP2, MMP8, MMP9, MMP12, MMP14 and MMP19.

As recently as 2007 and 2008, Lowrey and Turino document the need for further research. Consideration of all of this information sets forth a more than reasonable basis for finding that the specification does not enable the scope of the rejected claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-12 and 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Because L is required to be a divalent moiety, the monovalent groups (C2 to 6 alkynyl, C2 to 6 alkenyl, C1 to 6 alkyl, C1 to 6 heteroalkyl or C3 to 6 heteroalkynyl) cannot represent this variable. This insertion of the term "divalent" before each monovalent moiety does not cure the indefiniteness but adds to it. A monovalent group cannot be made into a divalent group thereby.
- The term "sulfonamino" fails to particularly point out and distinctly claim the intended subject matter. US 20040010022 states inconclusively that examples of sulfonamino groups include, but are not limited to, -NHS(=O)2CH3 and -N(CH3)S(=O)2 C6H5. Applicants state that "to the best of Applicants' knowledge," the term "alkylsulfonamino" is the correct nomenclature to describe a moiety "alkyl-SO2-N<." There is no definition or exemplification of "alkylsulfonamino" in the specification. To the best of examiner's knowledge, this is not a standard term and Applicants are requested to provide a standard definition thereof or cancel it from the claims.
- In the G1 substituents, it is not understood what is intended by "N,N-aminocarbonyl." The nomenclature "N,N-" usually precedes the definition of substituents on an amino group, however no such substituents are here defined.
- The second G1 definition "a bicyclic ring structure, a tricyclic ring structure or a tetracyclic ring structure, each ring in the bicyclic, tricyclic, or tetracyclic ring structure is, independently, joined to the next ring in the bicyclic, tricyclic, or

tetracyclic ring structure by a direct bond, by -O-, by divalent C1-6 alkyl, by divalent C1-6 haloalkyl, by divalent C1-6 heteroalkyl, by divalent C2-6 alkenyl, by divalent C2-6 alkynyl, by sulfone, by CO, by NR7CO, by CONR7, by NR7, by S, or by C(OH), or is fused to the next ring in the bicyclic, tricyclic, or tetracyclic ring structure" fails to particularly point out and distinctly claim intended subject matter, because it distorts the accepted chemical meaning of bicyclic, tricyclic or tetracyclic. A bicyclic ring structure contains two fused rings. Fusion can occur in three ways: at a single atom (spirocyclic), at two mutually bonded atoms, or across a sequence of atoms (bridgehead). See Wikipedia, <http://en.wikipedia.org/wiki/Bicyclic>, downloaded 1/21/2009. Tri- and tetra-cyclic ring structures are correspondingly understood. See Suzuki, et al., J. Mol. Biol. (2007) 372, 1204-1214, at 1205, showing cyclization of N1-methylguano-sine to the tricyclic ring structure imG-14. See Craft, et al., Tet. Ltrs. 49 (2008) 5931-5934, showing the tetracyclic ring structure of compound 19.

- Because the moieties listed as joining one G1 ring structure to the next G1 ring structure must be divalent, the monovalent groups (C1-6 alkyl, C1-6 haloalkyl, C1-6 heteroalkyl, C2-6 alkenyl, C2-6 alkynyl) cannot represent this variable. Insertion of the term "divalent" before each monovalent moiety does not cure the indefiniteness but adds to it. A monovalent group cannot be made into a divalent group thereby.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is

(571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CECILIA M. JAISLE

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624